Immunology 2017

The competitive nature of signal transducer and activator of transcription complex formation drives phenotype switching of T cells

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Abstract

© 2017 John Wiley & Sons Ltd. Signal transducers and activators of transcription (STATs) are key molecular determinants of T-cell fate and effector function. Several inflammatory diseases are characterized by an altered balance of T-cell phenotypes and cytokine secretion. STATs, therefore, represent viable therapeutic targets in numerous pathologies. However, the underlying mechanisms by which the same STAT proteins regulate both the development of different T-cell phenotypes and their plasticity during changes in extracellular conditions remain unclear. In this study, we investigated the STAT-mediated regulation of T-cell phenotype formation and plasticity using mathematical modelling and experimental data for intracellular STAT signalling proteins. The close fit of our model predictions to the experimental data allows us to propose a potential mechanism for T-cell switching. According to this mechanism, T-cell phenotype switching is the result of the relative redistribution of STAT dimer complexes caused by the extracellular cytokine-dependent STAT competition effects. The developed model predicts that the balance between the intracellular STAT species defines the amount of the produced cytokines and thereby T-cell phenotypes. The model predictions are consistent with the experimentally observed interferon-γ to interleukin-10 switching that regulates human T helper type 1/type 1 regulatory T-cell responses. The proposed model is applicable to a number of STAT signalling circuits.

http://dx.doi.org/10.1111/imm.12851

Keywords

Interferon-γ, Interleukin-10, Phenotype switching, Signal transducers and activators of transcription, T cells